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EXAMINER	
RAWLINGS, STEPHEN L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/995,529	WATKINS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121-158* is/are pending in the application.

4a) Of the above claim(s) *142-158* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-140* is/are rejected.

7)☒ Claim(s) *141* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTOL-461*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 20, 2007, has been entered.

1. The amendment filed March 20, 2007, is acknowledged and has been entered. Claims 89-120 have been canceled. Claims 121-158 have been added.

2. Claims 89-100 are pending in the application. Claims 142-158 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Election was made **without** traverse, as further explained below.

3. Claims 89-141 are currently under prosecution.

Grounds of Rejection Withdrawn

4. Applicant's amendment filed March 20, 2007, canceling all previously presented claims and adding claims 121-158 has rendered moot the rejections set forth in the previous Office action mailed August 30, 2006.

Response to Amendment

5. Applicant's arguments and/or remarks with respect to the grounds of rejection set forth in the preceding Office action have been considered but are moot.

Election/Restriction

6. As noted in the Office action mailed May 11, 2004, Applicant made a provisional election with traverse to prosecute the invention of claims 1-22 and 42, drawn to a grafted antibody or functional fragment thereof, which has specific binding activity for a cryptic collagen epitope, insofar as the claims are drawn to the species of antibody comprising SEQ ID NOs: 45, 155, 63, 157, 22, and 77. Affirmation of this election was made in the response filed November 12, 2004; however, because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). As further noted in the Office action, claim 43, drawn to a nucleic acid encoding the antibody of any of claims 1-22 and 42, was rejoined with the claims drawn to the elected invention; and therefore to that extent the restriction and election requirement has been withdrawn.

Applicant was advised in the Office action mailed May 11, 2004, that the claims would be considered during the prosecution on the merits of this application to the extent that those claims read on the elected species of invention, and to which extent the claims shall be restricted if no generic claim is finally held to be allowable. The Office action noted that a generic claim encompassing a novel and nonobvious species of invention may be allowable over the prior art, but not necessarily over 35 U.S.C. §§ 101 and 112.

7. Newly submitted claims 142-158 are directed to a species of invention that is independent or distinct from the elected species of invention originally claimed for the following reasons:

The elected species of invention is a grafted antibody or antigen binding fragment thereof comprising the three heavy chain CDRs of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77.

The species of invention to which newly added claims 142-158 are specifically directed are structurally distinct antibodies comprising one or more CDRs that differ from those of the elected species. Though each species of invention is an antibody or fragment thereof that binds denatured collagen, because of such structural dissimilarity, each species is patentably distinct from the others, including the elected species.

Because each of the species of invention to which newly added claims 142-158 is structurally distinct from the elected species of invention, the search necessary to consider claims directed to any one these species is different from the search that has been performed to examine claims directed to the elected species. Consequently, it would be a serious burden to have to examine any of the newly added claims because in each case a new and different search would have to be performed.

Since each of the species of invention to which newly added claims 142-158 and the elected species of invention are patentably distinct and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See M.P.E.P. §§ 803 and 809.

Since applicant has received an action on the merits for the originally presented invention, this species of invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 142-158 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

8. Claim 141 is objected to because the claim depends from claim 121, which is drawn to an antibody or antigen binding fragment thereof, which has higher binding affinity for denatured collagen over native collagen, yet redundantly recites, "which binds denatured collagen". The antibody that preferentially binds to denatured collagen with higher binding affinity than it does to native (non-denatured) collagen must necessarily bind to denatured collagen; so therefore the recitation of the limitation in claim 141 is redundant.

Appropriate correction is required.

Claim Rejections – 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 124-128 and 137-140 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 124-128 and 137-140 are vague and indefinite for the following reasons:

The claims 124-128 and 137-140, which depend from claims 121 and 131, respectively, are drawn to an antibody or antigen binding fragment thereof. According to claims 124-128 and 137-140 the antibody or antigen binding fragment comprises two or more "substitutions". Though claims 121 and 131 recite the limitation, "wherein at least one of the CDRs in the heavy chain variable region or the light chain variable region comprises one or more substitutions, it is not evident that the "substitutions" to which claims 124-128 and 137-140 are directed are necessarily one or more of the substitutions to which claim 121 or claim 131 is directed. Moreover, the "substitutions" to which claims 124-128 and 137-140 are directed are not necessarily amino acid substitutions, though perhaps implied. Mere implication, however, does not suffice to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as required under the provisions of 35 U.S.C. § 112, second paragraph. Furthermore, even if it were understood that the "substitutions" to which claims 124-128 and 137-140 are directed are amino acid substitutions, it would remain unclear if the substitutions occur in the CDRs or the framework of the variable domain of the antibody or fragment thereof, or perhaps in the constant domain, and whether or not those "substitutions" are necessarily selected from those specifically recited in the dependent claims. Because of the apparent ambiguity with the claims may be construed, it is submitted that they fail to delineate the metes and bounds of the subject matter that is regarded as the invention with the clarity and particularity necessary to satisfy the

requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 89-140 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Guidelines states that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). Guidelines continues:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate

> written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In this instance, the claims are directed to a genus of antibodies or antigen binding fragments thereof, which preferentially bind to denatured collagen with higher affinity than it does to native (non-denatured) collagen, wherein each member of the genus comprises a complementarity determining region (CDR) that is identical to a CDR of the prior art's monoclonal antibody designated "HUIV26" (i.e., the light chain's CDR2), or which is a variant of a CDR of monoclonal antibody HUIV26.

First described by Xu et al. (*Hybridoma*. 2000 Oct; **19** (5): 375-385) (of record), monoclonal antibody HUIV26 binds to denatured collagen, and little if any native (non-denatured) "triple-helical" collagen and therefore having a higher affinity for native (non-denatured) collagen than it does to denatured collagen.

Accordingly, the claims are drawn to this antibody that has been described by the prior art, as well as to variants of the prior art's monoclonal antibody, which comprise a

light or heavy chain CDR having an amino acid sequence that differs from the amino acid sequence of the corresponding CDR of the prior art's monoclonal antibody, but nonetheless has or retains the ability of the monoclonal antibody to bind preferentially to denatured collagen, as opposed to triple helical (native) collagen.

Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) (of record) reviews the structural basis of antigen-antibody recognition is reviewed. A naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

Accordingly, it is apparent that, though the claimed antibodies or antigen binding fragments thereof, with a notable exception explained below, comprise at least one CDR, which is a variant of the corresponding CDR of the prior art's monoclonal antibody HUIV26, they need not comprise any one or more CDRs that are identical to those of the remaining CDRs of monoclonal antibody HUIV26. For example, the claims encompass an antibody comprising a heavy chain variable region comprising a CDR1 having the amino acid sequence of SEQ ID NO: 26 (i.e., the amino acid sequence of the corresponding CDR of monoclonal antibody HUIV26), but for the substitution of the arginine at position 6 of this sequence by histidine; so, while this embodiment comprises a heavy chain CDR1 that is a variant of the heavy chain CDR1 of monoclonal antibody HUIV26, the remaining five CDRs need not comprise the amino acid sequences of the other CDRs of monoclonal antibody HUIV26, and need not comprise any of the amino acid sequences of the surrounding framework regions of the heavy or light chain of the monoclonal antibody. Therefore, because the function of the claimed antibody or antigen binding fragment thereof (i.e., its binding specificity and affinity) is dependent upon the amino acid sequences of the CDRs and framework regions (again, of the

amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant framework regions, and given the structural variability of the claimed genus, as a whole, it is apparent that there is no particularly identifying structural feature that is shared by the members of the genus, which correlates with, or accounts for their common ability to bind preferentially to denatured collagen, rather than to, or with decreased affinity for native (non-denatured) collagen.

As a consequence of the fact that the requisite binding activity of the claimed genus of antibodies or antigen binding fragments thereof, which distinguishes its members from the prior art's monoclonal antibody, cannot be attributed to a particularly identifying structural feature that is shared by members of the claimed genus of antibodies or antigen binding fragments thereof, the skilled artisan could not immediately envision, recognize or distinguish at least most of the antibodies or antigen binding fragments thereof encompassed by the claims.

Claims 121-130 are more broadly drawn to an antibody or antigen binding fragment thereof, whereas claims 131-140 are more narrowly drawn to a *grafted* antibody or antigen binding fragment thereof. While the term "grafted" is not explicitly defined, it is noted that the specification discloses: "For the specific example of CDR grafting, the parent molecule from which the grafted CDRs are derived is a donor molecule", where an acceptor molecule, including framework and/or other antibody fragments, is the receiving molecule into which the CDRs are grafted" (paragraphs [0023] and [0024] of the published application). With regard to the grafted antibody, the specification further explains that it is the donor CDRs confer binding affinity of the parent molecule onto the receiving molecule, and thus the acceptor antibody molecule or fragment is imparted with the binding affinity of the donor CDRs or parent molecule. Accordingly, claims 131-140 encompass, for example, a "humanized" antibody comprising the CDRs of a donor antibody having a particularly defined binding specificity and the framework regions and constant domains of a different antibody, not necessarily sharing the same binding specificity as that of the donor. Nonetheless, because the term "grafted" is not explicitly defined in a limiting manner, claims 131-140

are construed to include, but not limited to such recombinant antibodies that necessarily comprise a plurality of heterologous parts, which are derived from different antibodies.

The prior art teaches well-known and conventional methodology for "humanizing" monoclonal antibodies. For example, Gussow et al. (*Methods in Enzymology*. 1991; **203**: 99-121) teach the general methodology for making humanized antibodies; see entire document. One means for producing a humanized antibody involves grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced relatively early in the development of the art by Rudikoff et al. (*Proc. Natl. Acad. Sci. USA*. 1982; **79** (6): 1979-1983). Rudikoff et al. teaches that the alteration of a *single* amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of, or failure to retain the antigen binding specificity of the "parental" antibody by the variant; see entire document (e.g., the abstract). This sensitivity to such minor alterations is not an

anomaly, but rather has since been often been observed a prevalent, if not frequent phenomenon[1].

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA*. 1987 May; **84** (9): 2926-2930) (of record) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA*. 1989 Jul; **86** (14): 5532-5536) (of record) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) (of record) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

Despite such evident unpredictability, and the fact that certain amino acid residues within the framework regions, as opposed to the CDRs, may have importance in determining the specificity and/or affinity of an antibody for an antigen, there is near consensus in the art that the specificity of the antibody is most dependent upon the identities of the CDRs. Vajdos et al. (*J. Mol. Biol.* 2002 Jul 5; **320** (2): 415-428), for example, states that antigen binding is primarily mediated by the CDRs more highly

[1] See, e.g., Winkler et al. (*J. Immunol.* 2000 Oct 15; **165** (8): 4505-4514), describing changing the

conserved framework segments, which connect the CDRs, are mainly involved in supporting the CDR loop conformations, and in *some cases* framework residues also contact antigen; see entire document (e.g., page 416, column 1).

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Although collagen may rightfully be considered a fully characterized antigen, the claims are not directed to just antibody that binds collagen, but rather to an antibody that binds preferentially to *denatured* collagen. Moreover, the claims are directed to a genus of antibodies or antigen binding fragments thereof that have a binding activity that differs from other antibodies disclosed by the prior art that commonly bind collagen, since the claimed antibodies bind with relatively increased affinity to denatured collagen, and bind only poorly, if at all, to native, triple helical (non-denatured) collagen.

The epitope to which the claimed antibody binds has not been characterized, nor as discussed in preceding Office actions can it be easily identified. Because of its apparent absence or inaccessibility, where the collagen molecule has not been denatured, the specification terms the epitope "cryptic"; see, e.g., paragraph [0036] of the published application[2]. Therefore, recognizing an antibody that is encompassed by the claims is not a mere matter of determining whether the antibody binds to a well characterized antigen, such as collagen, but rather determining relatively *how well* it binds to a cryptic, uncharacterized and perhaps non-uniform epitope of denatured collagen. So, the affinity, as well as the specificity of the claimed antibody, must be considered in determining whether any given antibody might infringe the claims, and whether or not the description of the genus, and any particular species of antibody

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specificity of an antibody by single point mutations (entire document; e.g., the abstract).

disclosed in this application, would reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Therefore, it is aptly noted that, while in some cases the framework residues may only marginally contribute to the antigen binding specificity of an antibody, it appears that these residues are generally more critical to determining the affinity of the antibody (i.e., the strength by which the antibody binds to the antigen[3]). Similarly, although there is considerable evidence that the variable domain of the heavy chain, as opposed to that of the light chain, may be more important for the specific interaction of the antibody with an antigen, it appears that the light chain has a substantial role in determining the affinity of the interaction[4].

Despite these facts, the claims are directed to a genus of antibodies that comprise a heavy chain or a light chain variable region comprising at least one CDR that is a variant of the corresponding CDR of monoclonal antibody HUIV26, or alternatively at least a light chain CDR2, which is identical to that of the monoclonal antibody, but which otherwise need not comprise CDRs or framework regions that are identical to the CDRs and framework regions of the monoclonal antibody. So, for example, while the claimed variant might comprise the heavy chain CDR3 of monoclonal antibody HUIV26, the others CDRs and the surrounding framework regions might be derived from any other antibody; yet it is now well understood that, most generally, retention of one, and only one CDR (e.g., the heavy chain CDR3) will not produce a variant having an increased, or even the same binding affinity, nor will it necessarily bind to the same antigen.

De Pascalis et al. (*J. Immunol.* 2002; 169 (6): 3076-3084), for example, describes demonstrating by CDR grafting that, while perhaps not directly contacting the antigen, certain framework residues are essential to the preservation of the structural integrity of the antigen binding site; see entire document (e.g., page 3079, column 2).

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[2] U.S. Patent Application Publication No. 2003/0099655 A1.
[3] See the specification at paragraph [0033] of the published application (U.S. Patent Application Publication No. 2003/0099655 A1), which defines the term "binding affinity".
[4] See, e.g., Lopez-Requena et al. (*Mol. Immunol.* 2007; **44**: 1015-1028) (entire document; e.g., the abstract).

Having realized the role of the framework residues, Wu et al. *(J. Mol. Biol.* 1999 Nov 19; **294** (1): 151-162) discloses the finding that it is difficult to predict which framework residues serve critical roles in maintaining the antibody's affinity and specificity, due in part to the large conformational change that occur in the antibody upon its interaction with the antigen; see entire document (e.g., page 152, column 1).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by the disclosure, for example, of Casset et al. (*Biochem. Biophys. Res. Commun.* 2003 Jul 18; **307** (1): 198-205). Casset et al. describes the rational design and construction of a peptide mimetic of an anti-CD4 monoclonal antibody binding site; see entire document (e.g., the abstract). The peptide mimetic was designed with 27 residues formed by inclusion of residues from five of the six CDRs of the antibody; see, e.g., the abstract. Casset et al. states that although the heavy chain CDR3 is at the center of most, if not all antigen interactions, clearly other CDRs play an important role in the recognition process; see, e.g., page 199, column 1. This conclusion is apparent given their demonstration that an active peptide mimetic that retains the ability to bind to the antigen necessarily comprises amino acids derived from all CDRs, except the light chain CDR2, in addition to a framework residue located just before CDR3 of the antibody's heavy chain; see, e.g., page 202, column 1. Though Casset et al. concedes that perhaps not all of the residues representing the various different CDRs will ultimately prove essential to the interaction, it will not be without further extensive studies that such a realization may be made (page 202, column 1).

The art of engineering functional recombinant antibodies, such as the grafted antibodies to which the claims are directed, is even more confounded by findings that residues, which are positioned outside the recognized boundaries of the canonical CDRs, may contribute substantially to the interaction of an antibody and an antigen. For example, MacCallum et al. (*J. Mol. Biol.* 1996 Oct 11; **262** (5): 732-745) describes the discovery that although the residues of CDR3 of the heavy and light chains are dominant determinants of the interaction, a number of essential residues contacting the antigen have been placed outside the regions that are recognized using the

conventional or standard definitions of the CDRs, which are generally used to define the components of the antigen binding site of the antibody; see entire document (e.g., page 733, column 2). Moreover, MacCallum et al. teaches an appreciation of the fact that residues within the CDRs that do not actually make contact with the antigen may be important because of their contributions to the conformation of the antibody's antigen recognition site; see, e.g., page 735, column 1.

Making further apparent the unpredictability of the importance of residues within the CDRs and other parts of an antibody, which must instead be determined empirically, Holm et al. (*Mol. Immunol.* 2007 Feb; **44** (6): 1075-1084) describes the mapping of residues important to the interaction of an anti-cytokeratin antibody with the antigen, where although residues in the CDR3 of the heavy chain were determined to be essential, they disclose their *unexpected* finding that a residue in CDR2 of the light chain forms a necessary part of the antigen binding site of the antibody contacting the antgen; see entire document (e.g., the abstract). Thus, as recently as 2007, there are reports indicating despite the progress made toward understanding the interactions of antibodies and antigens, because of the unpredictable nature of the art, much information concerning the specificity and/or affinity of any given antibody cannot be gleaned by a causal examination and analysis of its structure, but must instead be gathered by rigorous, albeit perhaps routine, experimentation.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, Applicant is reminded, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, it is submitted that there is no language that adequately describes with the requisite clarity and particularity the genus of antibodies and antigen binding fragments, as a whole, to which the claims

are now directed. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

The claims encompass species of antibodies that are described only as having a particular function, but not necessarily having any particular structure accounting for that function. For example, the claims encompass an antibody that varies structurally from the prior art's monoclonal antibody designated "HUIV26", despite having a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22 or perhaps a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 63. Yet, there is no factual evidence of record supporting Applicant's position that any such antibody comprising a light chain variable region comprising the CDR2 of SEQ ID No: 22 or a heavy chain variable region comprising the CDR3 of SEQ ID NO: 63 has or retains the binding activity of monoclonal antibody HUIV26.

The Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to inhibit an activity of BMP-2 to achieve therapeutic effect, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods

from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). If the skilled artisan cannot immediately envision, recognize or distinguish at least a substantial number of the antibodies having the requisite structure and function, which are encompassed by the claims, then, the specification cannot have adequately described the genus, as a whole, in a manner and to a degree sufficient to permit the artisan to know or determine whether any given antibody infringes those claims; and therefore the specification would not reasonably convey to the artisan that Applicant had possession of the genus at the time the application was filed, so as to fulfill the requirement set forth under 35 U.S.C. § 112, first paragraph.

In addition, although the skilled artisan could potentially identify an antibody that might be encompassed by the claims using fairly routine methodology to screen candidate antibodies encoded by a library of coding sequences, for example, to determine if the antibody has the ability to bind preferentially to denatured collagen, the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Guidelines further states, "[f]or inventions in an unpredictable

art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Moreover, because the claims encompass a genus of antibodies or antigen binding fragments thereof, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a *representative* number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

As explained in the preceding Office action, the specification teaches two species of antibody, in particular, that are variants of monoclonal antibody HUIV26, which demonstrably have the requisite preferential binding activity for denatured collagen over native collagen[5], namely "2D4H1-C3" and "DhuG5"; see, e.g., Figure 8.

The specification further discloses in the table set forth as Figure 4C the single amino acid substitutions that were found to be "beneficial" following the introduction of random mutations in the CDRs of either the light or heavy chain variable regions of the Fab of monoclonal antibody HUIV26 (i.e., "wild-type Fab"). The specification discloses such "beneficial" mutations are those producing variants of the wild-type Fab of monoclonal antibody HUIV26 that bind to denatured collagen with higher affinity, relative to the corresponding wild-type Fab, as demonstrated by ELISA; see, e.g., page 87, lines 12-15. For example, the table in Figure 4C indicates that the replacement of

the naturally occurring serine at position 35 of the first CDR of the heavy chain polypeptide of monoclonal antibody HUIV26 (i.e., the amino acid at position 10 within the amino acid sequence of the CDR set forth as SEQ ID NO: 26) by threonine, alanine or glycine is "beneficial". Such variants therefore have or retain the ability of the parental, wild-type monoclonal antibody to bind preferentially to denatured type IV collagen, and perhaps have even higher affinities than the wild-type. Notably, the table set forth in Figure 4C includes the two species described by Figure 8 as having at least 2 fold greater binding affinity for denatured collagen, as compared to their binding affinities for native (non-denatured) collagen; again, these variants are a particular embodiment of elected species, designated "DhuG5", and the variant designated "2D4H1-C3".

However, in contrast to the breadth of this disclosure of the "beneficial mutants" described by Figure 6, the claims are directed to a genus of antibodies, which are not, per se, variants of the prior art's monoclonal antibody. Whereas all of the disclosed "beneficial mutants" are variants of the prior art's monoclonal antibody HUIV26, which apparently differ, at least in part, at one or more of the indicated sites in the heavy or light chain variable region by amino acid substitutions, but which otherwise comprise variable regions that are not substantially unlike that of the monoclonal antibody, substantial portions of the claimed antibodies, including the variable regions and CDRs might not derive from the amino acid sequences of light and/or heavy chains of monoclonal antibody HUIV26. Again, the claims merely require the antibody or antigen binding fragment to comprise at least one, but not necessarily each of the "substitutions" specified therein; so, for example, an antibody comprising a light chain CDR3 having the amino acid sequence of SEQ ID NO: 63, a single amino acid variant of the naturally occurring CDR3 of the light chain of monoclonal antibody HUIV26, but which otherwise comprises a structure that is entirely unlike the monoclonal antibody is encompassed by the claims. Yet, as discussed in detail in the paragraphs above, an antibody having, or retaining a single CDR, or moreover a variant of a naturally occurring CDR, would not

[5] That is, these variants have at least 2 fold greater affinity for denatured collagen, as compared to their

be reasonably be expected to have the same antigen binding properties as any other antibody comprising the same CDR, or that which is naturally occurring. Accordingly, it cannot be predicted whether an antibody that might be encompassed by the claims, because it happens to have the recited functional feature, will have *any* particular binding specificity and/or affinity, much less the actual binding activity that is required by the claims.

Furthermore, since the "combinatorial mutants" disclosed in Figure 6 as having equivalent or enhanced binding activity comprise a plurality of substitutions in one or more of the CDRs of the light and/or heavy chain variable regions of monoclonal antibody HUIV26, in many instances, it is not known, nor can it be predicted whether a variant having an amino acid sequences with only one or two of such substitutions will have the requisite binding activity. It does not appear that the effect of each substitution has been independently determined.

In addition, it is submitted that even were such a determination made, the information gathered would still not be sufficient to permit one to know the influence or contribution of any one substitution in the presence of another. The additive or synergistic effects of any given plurality of substitutions cannot be used as predictive indication of the effects that other substitutions or pluralities thereof might have upon the antibody's structure and/or function. This is because one substitution might cause a change in the structure and/or function of the variant, which is altered by the change in its structure and/or function caused by yet another substitution. In general, such complexity prevents the artisan from predicting the outcome of multiple substitutions, which must instead be determined empirically.

Though the present claims do not require the antibody or antigen binding fragment thereof to bind more strongly to denatured collagen, as compared to monoclonal antibody HUIV26, it is evident that the structural differences between the prior art's monoclonal antibody and any of the disclosed antibodies having relatively increased binding activity must account for such enhanced binding activity. For

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binding affinities for native (non-denatured) collagen.

example, one of the two variants of monoclonal antibody HUIV26 (i.e., "2D4H1-C3"), which demonstrably has increased binding activity, comprises a heavy chain variable region comprising the first, second, and third CDRs of SEQ ID NO: 46, SEQ ID NO: 28, AND SEQ ID NO: 63, respectively, and a light chain variable region comprising the first, second, and third CDRs of SEQ ID NO: 20, SEQ ID NO: 22, and SEQ ID NO: 77, respectively. Then, as apparently depicted in Figure 6[6], the second of these variants having increased preferential binding activity relative to the prior art's monoclonal antibody, namely the species designated "DhuG5"[7] comprises a heavy chain variable region comprising a first, second, and third CDR differing from the corresponding CDRs of monoclonal antibody HUIV26 by one or two substitutions and a light chain variable region comprising a first CDR differing from the corresponding CDR of monoclonal antibody HUIV26 by three substitutions, the second CDR of the monoclonal antibody, and a third CDR differing from the corresponding CDR of the monoclonal antibody by one substitution. Although the elected species of antibody comprises a heavy chain variable region comprising the same third CDR as the variant designated "2D4H1-C3", which has the requisite preferential binding activity for denatured collagen, *the heavy chain of the elected species of antibody comprises a different first and second CDR* (i.e., a CDR1 having the amino acid sequence set forth as SEQ ID NO: 45, as opposed to the amino acid sequence of SEQ ID NO: 46, and a CDR2 having the amino acid sequence set forth as SEQ ID NO: 155, as opposed to the amino acid sequence of SEQ ID NO: 28). Furthermore, although the elected species of antibody comprises a light chain variable region comprising the same second and third CDRs as the variant designated "2D4H1-C3", *the light chain comprises a different first CDR* (i.e., a CDR1 having the amino acid sequence set forth as SEQ ID NO: 157, as opposed to the amino

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[6] Note Applicant's remark (item #5) at page 9 of the amendment filed November 16, 2006, which asserts the structure of "DhuG5" is indicated by the information disclosed in Figure 6.

[7] Notably, this species designated "DhuG5" is the elected species (i.e., the antibody, or functional fragment thereof, which comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77); and according to Figure 6, other species of antibody sharing the structural features of the elected species of invention include those designated "DcomD7" and "DhuH8", though notably the structural and/or functional differences between these three presumably distinct antibodies is not apparently disclosed.

acid sequence of SEQ ID NO: 20). Though perhaps vastly oversimplified, given the evident complexity and unpredictability of the art, it is submitted that the features that are not unlike those of the prior art's monoclonal antibody are not likely to account for the differential binding activities of the disclosed variants thereof (i.e., "2D4H1-C3" and "DhuG5") that demonstrably bind preferentially to denatured collagen. Rather, the functional differences between monoclonal antibody HUIV26 and these variants thereof are more likely than not to be attributable to the difference in their structures. As such, the only structurally different features that might account for any differential binding activity, as compared to monoclonal antibody HUIV26, which is shared by the variant designated "2D4H1-C3" and the elected species of invention is the identity of the third CDR of the heavy chain and the identity of the third CDR of the light chain. While it might be understood that that variation in one or both of the first and third CDRs of the heavy chain and/or the variation in the third CDR of the light chain of the variants designated "2D4H1-C3" and "DhuG5" is likely to account for the observed differential binding activity of the variants, as compared to monoclonal antibody HUIV26 (see, e.g., Figure 8), it is not known, and cannot be predicted whether the variation in the third CDR of the heavy chain alone might account for this differential binding activity[8].

Given the marked structural dissimilarity of the members of the genus of antibodies or antigen binding fragments thereof, which are encompassed by the claims, it is apparent that the two species of antibody that are demonstrated to have enhanced binding activity are not representative of the genus, as a whole, since, for example, though both species comprise an identical light chain CDR3 and an identical heavy chain CDR2, the claimed antibodies and fragments thereof need not comprise these same structural features. Though it is not evident that their shared features alone account for their similar binding activities, *were* the variants designated "2D4H1-C3" and "DhuG5" properly, if not reasonably considered representative of the genus, as a whole, the claimed antibodies and fragments thereof might necessarily comprise those

[8] Here, Applicant is reminded of the teachings of MacCallum et al. and Holm et al. (*supra*), and their unexpected findings that residues outside CDR3 contribute substantially to the interaction of the antibody and antigen.

particular structural features. However, as explained, it is apparent that there is no particularly identifying structural feature that is necessarily shared by the members of the claimed genus of antibodies or fragments thereof, which correlates with, or accounts for their common ability to bind preferentially to denatured collagen, rather than or with decreased affinity for native (non-denatured) collagen.

For these reasons, it cannot be predicted whether any of the other variants of the prior art's monoclonal antibody will bind preferentially to a "cryptic" epitope of collagen that is either inaccessible or absent unless first denatured, so as to bind more strongly to denatured collagen than to native (non-denatured) collagen; for this reason, the claimed invention cannot be immediately envisioned, recognized or distinguished from other antibodies or fragments thereof. Moreover, only after empirically determining whether or not any given antibody or antigen binding fragment thereof, which has the necessary structure, has the requisite binding activity, would it become evident that the antibody or antigen binding fragment thereof infringes the claims. Accordingly, the specification cannot have described the claimed genus, as a whole, with the requisite clarity and particularity to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Finally, whereas the claims are directed to an antibody or antigen binding fragment thereof that preferentially binds to denatured "collagen", as opposed to native "collagen", Xu et al. (*J. Cell. Biol.* 2001 Sep 3; **154** (5): 1069-1079) (of record) teaches although monoclonal antibody HUIV26 binds denatured type IV collagen, it is incapable of binding other denatured forms of collagen, including types I, II, III, and V; see entire document (e.g., page 1070, column 2). Consistently, Roth et al. (*Am. J. Pathol.* 2006 May; **168** (5): 1576-1586) suggests that monoclonal antibody HUIV26 binds exclusively to denatured type IV collagen *in vivo*, without binding to denatured type I collagen; see entire document (e.g., page 1579, column 1). Accordingly, it appears the antigenic determinant recognized by monoclonal antibody HUIV26, the "cryptic epitope" may be a unique feature of denature type IV collagen.

At best, the disclosure would provide an adequate written description of relatively fewer antibodies or antigen binding fragments thereof, which are described with the

requisite clarity and particularity by Figures 4C and 6, as opposed to the far greater number of antibodies or antigen binding fragments thereof to which the present claims are directed; and therefore, it is suggested that Applicant consider amending the claims such their breadth is more commensurate with the breadth of the proposed claim set forth below.

13. Claims 121-140 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an antibody or antigen binding fragment thereof, which binds to denatured type IV collagen, having a higher binding activity for denatured type IV collagen over native type IV collagen, wherein said antibody or functional fragment comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 46, SEQ ID NO: 28, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 20, SEQ ID NO: 22, and SEQ ID NO: 77, and a nucleic acid molecule encoding said antibody, **for making and using** an antibody or antigen binding fragment thereof, which binds to denatured type IV collagen, having a higher binding activity for denatured type IV collagen over native type IV collagen, wherein said antibody or functional fragment comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77, and a nucleic acid molecule encoding said antibody, **and for making and using** any antibody encompassed by the claims, which is taught by the prior art (e.g., monoclonal antibody HUIV26), **does not reasonably provide enablement for making and using** any antibody or antigen binding fragment thereof encompassed by the generic claims, or any nucleic acid molecule encoding said antibody, wherein said antibody is *not* a variant of the prior art's monoclonal antibody HUIV26 that binds to denatured type IV collagen with increased affinity relative to native type IV collagen, which comprises a light and/or heavy chain variable region comprising any one or more of the "beneficial" mutations to one or more of the CDRs of the monoclonal antibody, which are disclosed by the specification's Figure 4C and/or Figure

6, and which otherwise comprises CDRs that are identical to the corresponding CDRs of the monoclonal antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

For the reasons set forth in the above rejection of the claims as failing to satisfy the written description requirement, it is not known, and cannot be predicted which antibodies or antigen binding fragments thereof, which comprise the structural feature(s)

recited in the claims, will have the requisite binding activity. Accordingly, because it would be necessary to first make any of such antibodies or antigen binding fragments, which might be encompassed by the claims, and then empirically determine whether it has the requisite binding activity, the claimed invention cannot be made and/or used without undue and/or unreasonable experimentation.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Given the lack of correlation between the structural feature(s) of the claimed antibody and their common ability to bind preferentially bind to denatured collagen, as opposed to native (non-denatured) collagen, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify an antibody or antigen binding fragment having the requisite activity; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC §§ 102 and/or 103

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 121 and 131 are rejected under 35 U.S.C. 102(a) as being antipated by Xu et al. (*J. Cell Biol.* 2001 Sep 3; **154** (5): 1069-1079) (of record).

Claims 121 and 131 are drawn to an antibody or antigen binding fragment thereof comprising a heavy chain variable region and a light chain variable region, wherein at least one of the CDRs in the heavy chain variable region or the light chain variable region comprises a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22.

Although claim 131 is drawn to a *grafted* antibody, the term "grafted" is not explicitly defined in the specification in a limiting manner. If this term were considered to limit the manner in which the antibody is produced, the claim is construed as a product-by-process claim, thereby reading on an antibody that is produced recombinantly by a process that comprises grafting (i.e., inserting) the CDRs of the antibody into sites within the framework of the heavy or light chain variable regions of the antibody. However, while claim 131 would encompass, for example, a "humanized" antibody, it is submitted that the claim is not limited to such an antibody that comprises heterologous parts derived from different antibodies.

Xu et al. teaches a monoclonal antibody, which are designated "HUIV26"; see entire document (e.g., the abstract). Xu et al. teaches this monoclonal antibody recognizes a cryptic epitope within type IV collagen from a variety of species, but does not bind to triple helical (native) collagen; see, e.g., page 1077, column 1.

Because this antibody, which is disclosed by the prior art, comprises a light chain variable domain comprising a second CDR comprising the amino acid sequence of SEQ ID NO: 22, it cannot be distinguished materially, structurally or functionally from the antibody to which the claims are directed.

16. Claims 121, 131, 127, and 140 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al. (*Hybridoma*. 2000 Oct; **19** (5): 375-385) (of record).

Claims 121 and 131 are drawn to an antibody or antigen binding fragment thereof comprising a heavy chain variable region and a light chain variable region, wherein at least one of the CDRs in the heavy chain variable region or the light chain variable region comprises a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22. Claims 127 and 140 are drawn to the antibody of claims 121 and 131, respectively, wherein the antibody comprises five or more substitutions.

Although claim 131 is drawn to a *grafted* antibody, the term "grafted" is not explicitly defined in the specification in a limiting manner. If this term were considered to limit the manner in which the antibody is produced, the claim is construed as a product-by-process claim, thereby reading on an antibody that is produced recombinantly by a process that comprises grafting (i.e., inserting) the CDRs of the antibody into sites within the framework of the heavy or light chain variable regions of the antibody. However, while claim 131 would encompass, for example, a "humanized" antibody, it is submitted that the claim is not limited to such an antibody that comprises heterologous parts derived from different antibodies.

Xu et al. teaches a monoclonal antibody, which are designated "HUIV26"; see entire document (e.g., the abstract). Xu et al. teaches this monoclonal antibody recognizes a cryptic epitope within type IV collagen from a variety of species, but does not bind to triple helical (native) collagen; see, e.g., page 1077, column 1.

Because this antibody, which is disclosed by the prior art, comprises a light chain variable domain comprising a second CDR comprising the amino acid sequence of SEQ ID NO: 22, it cannot be distinguished materially, structurally or functionally from the antibody to which the claims are directed.

In addition, Xu et al. teaches a monoclonal antibody, which are designated "HUI77"; see entire document (e.g., the abstract). Xu et al. teaches this monoclonal antibody binds to denatured type IV collagen, but shows little if any reactivity with triple helical (native) collagen; see, e.g., the abstract.

Though monoclonal antibody HUI77 does not comprise a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22, absent a showing of any difference, the antibody is deemed materially, structurally and functionally indistinguishable from the antibodies to which claims 127 and 140 are directed.

17. Claims 121, 123, 127, 129-131, 133, 135, 136, and 140 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/40597 A1 (of record).

Claims 121 and 131 are drawn to an antibody or antigen binding fragment thereof comprising a heavy chain variable region and a light chain variable region, wherein at least one of the CDRs in the heavy chain variable region or the light chain variable region comprises a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22. Claims 127 and 140 are drawn to the antibody of claims 121 and 131, respectively, wherein the antibody comprises five or more substitutions. Claims 123 and 133 are drawn to the antigen binding fragments of claims 121 and 131, respectively, wherein the fragment is Fv, Fab, or $F(ab)_2$. Claims 129 and 130 are drawn to the antibody or fragment thereof of claim 121, wherein the antibody or fragment thereof comprises a therapeutic or diagnostic moiety, respectively; whereas claims 135 and 136 are drawn to the antibody or fragment thereof of claim 131, wherein the antibody or fragment thereof comprises a therapeutic or diagnostic moiety, respectively.

Although claim 131 is drawn to a *grafted* antibody, the term "grafted" is not explicitly defined in the specification in a limiting manner. If this term were considered to limit the manner in which the antibody is produced, the claim is construed as a product-by-process claim, thereby reading on an antibody that is produced recombinantly by a process that comprises grafting (i.e., inserting) the CDRs of the antibody into sites within the framework of the heavy or light chain variable regions of the antibody. However, while claim 131 would encompass, for example, a "humanized"

antibody, it is submitted that the claim is not limited to such an antibody that comprises heterologous parts derived from different antibodies.

WO 00/40597 A1 (Brooks et al.) teaches a monoclonal antibody, which are designated "HUIV26"; see entire document (e.g., the abstract). Brooks et al. teaches this monoclonal antibody recognizes denatured type IV collagen, but does not bind to triple helical (native) collagen; see, e.g., page 18, lines 3-5; and page 22, lines 9-11. Brooks et al. teaches antigen binding fragments of this and other antibodies; see, e.g., page 23, lines 1-5. Brooks et al. teaches immunoconjugates comprising these antibodies and further comprising diagnostic and/or therapeutic moieties; see, e.g., page 40, lines 14-19.

Because monoclonal antibody HUIV26 comprises a light chain variable domain comprising a second CDR comprising the amino acid sequence of SEQ ID NO: 22, it cannot be distinguished materially, structurally or functionally from the antibody to which the claims are directed.

In addition, Brooks et al. teaches two other monoclonal antibodies, which are designated "HUI77" and "XL313; see entire document (e.g., the abstract). Brooks et al. teaches both of these monoclonal antibodies bind to denatured collagen, but shows little if any reactivity with triple helical (native) collagen; see, e.g., Figure 28; page 18, lines 3-5; page 22, lines 9-11; and page 50, lines 13-15.

Though neither monoclonal antibody HUI77 nor monoclonal antibody XL313 is believed to comprise a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22, absent a showing of any difference, the antibodies are deemed materially, structurally and functionally indistinguishable from the antibodies to which claims 127 and 140 are directed.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 128 and 134 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over WO 00/40597 A1 (of record).

Claims 128 and 134 are drawn to a nucleic acid molecule encoding an antibody or antigen binding fragment thereof according to claims 121 and 131, respectively.

WO 00/40597 A1 (Brooks et al.) teaches that which is set forth in the above rejection of claims 121, 123, 127, 129-131, 133, 135, 136, and 140 under 35 U.S.C. 102(b).

In addition, Brooks et al. teaches the disclosed antibodies include "humanized" antibodies, which are produced by methodology that is both well known and conventional in the art.

Therefore, although Brooks et al. does not explicitly teach a nucleic acid molecule encoding the antibody or antigen binding fragment thereof, because Brooks et al. teaches the antibodies are "humanized", the disclosure necessarily described such a nucleic acid molecule.

If the disclosed subject matter is not deemed anticipatory of the claimed subject matter, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to make and use a nucleic acid molecule encoding the "humanized" antibody or antigen binding fragment thereof, simply because the well known and conventional methodology that is utilized to do so involves the production of just such nucleic acid molecules. Thus, it stands to reason that the ordinarily skilled artisan at the time the invention was made would have been motivated to make and use the nucleic acid molecule to make the humanized antibody or fragment thereof that would be encoded thereby, particularly because the prior art teaches the antibodies or their antigen binding fragments thereof are therapeutically and diagnostically useful.

Allowable Subject Matter

20. The following claim[9] drafted by the Examiner, which is considered to distinguish patentably over the art of record and which, given the instant disclosure, is deemed to satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph, is presented to Applicant for consideration:

Claim 121. An antibody, or antigen-binding fragment thereof, which is a variant of monoclonal antibody HUIV26 having one or more complementary determining regions (CDRs) having an amino acid sequence differing from the corresponding CDRs of monoclonal antibody HUIV26, and which has higher binding activity for denatured type IV collagen over native type IV collagen comprising a heavy chain variable region and a light chain variable region, wherein ~~at least one of the CDRs of the heavy chain variable region or the light chain variable comprises one or more substitutions selected from~~ said heavy chain variable region comprises:

(i) a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 26 or the amino acid sequence of SEQ ID NO: 26 but for ~~having~~ one or more substitutions o selected from the group consisting of:

(a) substitution of arginine at position 6 therein by histidine;

(b) substitution of methionine at position 9 therein by isoleucine; and

(c) substitution of serine at position 10 therein by threonine, alanine or glycine;

(ii) a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 28 or the amino acid sequence of SEQ ID NO: 28 but for ~~having~~ one or more substitutions o selected from the group consisting of:

(a) substitution of isoleucine at position 9 therein by alanine, serine or valine;

(b) substitution of serine at position 14 therein by tyrosine, alanine, histidine or glycine;

(c) substitution of lysine at position 16 therein by aspartic acid or glutamine; and

(d) substitution of aspartic acid at position 17 therein by lysine or serine; and

(iii) a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 30 or the amino acid sequence of SEQ ID NO: 30 but for ~~having~~ one or more substitutions o selected from the group consisting of:

(a) substitution of aspartic acid at position 3 therein by proline, glycine, threonine, or alanine;

(b) substitution of glycine at position 4 therein by proline, alanine, or histidine; and

(c) substitution of tyrosine at position 11 therein by proline or asparagine;

and wherein said light chain variable region comprises:

(iv) a light chain CDR1 having the amino acid sequence of SEQ ID NO: 20 or the amino acid sequence of SEQ ID NO: 20 but for ~~having~~ one or more substitutions o selected from the group consisting of:

(a) substitution of glutamine at position 4 therein by arginine or serine;

(b) substitution of asparagine at position 8 therein by serine; and

(c) substitution of serine at position 9 therein by tyrosine, tryptophan, histidine or arginine;

(d) substitution of glycine at position 10 therein by tyrosine, arginine, histidine or isoleucine; and

(e) substitution of glutamine at position 12 therein by lysine;

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[9] The claim has been marked to show the changes that are proposed relative to the present version of the claim.

(v) a light chain CDR2 having the amino acid sequence of SEQ ID NO: 22; and

(vi) a light chain CDR3 having the amino acid sequence of SEQ ID NO: 24 or the amino acid sequence of SEQ ID NO: 24 but for ~~having~~ one or more substitutions o selected from the group consisting of:

(a) substitution of serine at position 5 therein by glutamine, glycine, leucine, alanine, threonine or valine; and

(b) substitution of tyrosine at position 6 therein by asparagine, serine, proline and methionine.

21. The following is a statement of reasons for the above indication of allowable subject matter:

Written support for the proposed claim is found throughout the specification, as filed, but most notably in Figures 2C, 4C, and 6, which describe an embodiment of the claimed antibody or antigen binding fragment thereof, which is a variant of the prior art's monoclonal antibody, but for the substitution of one or more amino acids in any of the CDRs except for CDR2 of the light chain, but has or retains the ability of the monoclonal antibody to bind preferentially to denatured type IV collagen, as opposed to native (non-denatured, triple helical) collagen. Support for this functional limitation is found, e.g., in Figure 8 and its brief description at paragraph [0016] of the published application.

Each of the changes that may occur in the amino acid sequences of the heavy and/or light chain variable regions of the antibody or antigen binding fragment thereof, which is encompassed by the of the proposed claim, relative to those of monoclonal antibody HUIV26, is indicated to be "beneficial" by either Figure 4C or Figure 6, or both. The specification describes these "beneficial" amino acid substitutions as producing antibodies that bind to denatured collagen with higher affinity, as compared to the corresponding wild-type Fab of monoclonal antibody HUIV26, as demonstrated by ELISA; see, e.g., page 87, lines 12-15. Thus, if not possessing a relatively increased affinity for denatured type IV collagen, the claimed antibody or antigen binding fragment

thereof is expected to at least have or retain the function of the parental, wild-type antibody, binding preferentially to denatured collagen, as opposed to native collagen.

It is believed that antibodies or antigen binding fragments thereof, which are have the structural features of the claimed antibody or antigen binding fragment thereof, may lack the activity of monoclonal antibody HUIV26 to bind preferentially to denatured type IV collagen, as opposed to native collagen. However, a disclosure of every operable species is not required, even in unpredictable arts[10]; and furthermore, although the art of engineering recombinant antibodies to have or retain particular binding specificity and/or affinity is highly unpredictable, there are a finite number of antibodies comprising the requisite structural features, each of which is readily envisioned, and each of which could be made without undue or unreasonable experimentation. Therefore, given the fact than at least two antibodies having the required structural features (i.e., the variants designated "2D4H1-C3" and "DhuG5") have demonstrably been shown to the requisite activity, it is submitted the disclosure should be considered to reasonably enable one skilled in the art to make and use the claimed invention. The occurrence of some "non-working" antibodies, which although comprising the requisite structural features of the claimed antibody, lack its ability to bind preferentially to denatured type IV collagen, should be permitted under such circumstances.

Additionally, the Examiner finds no factual evidence teaching or reasonably suggesting any particular embodiment of the proposed claim will lack the requisite functional activity. See *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) ("[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.")

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[10] See M.P.E.P. § 2164.03.

For clarity, in contrast to the breadth of the proposed claim, the presently rejected claims are much more broadly drawn to an antibody or antigen binding fragment thereof that would not be so readily recognized by the artisan as a variant of the prior art's monoclonal antibody HUIV26. Again, the rejected claims are drawn to an antibody that need only comprise a light or heavy chain variable region comprising the light chain CDR2 of the monoclonal antibody and/or a variant of one or more of the other CDRs of the monoclonal antibody, but which may otherwise have a structure that differs entirely from that of the monoclonal antibody. Accordingly, the skilled artisan could not immediately envision the structures of each of the monoclonal antibodies or antigen binding fragments thereof that are encompassed by the claims, nor could the artisan predict which might have the requisite function; but in contrast to the breadth of the proposed claim, it is expected that a substantial number of antibodies having the requisite structural feature(s) would not bind to collagen, denatured or otherwise, or would lack the ability to bind preferentially to denatured collagen.

Conclusion

22. No claim is allowed.

23. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Pernasetti et al. (*Int. J. Oncol.* 2006 Dec; 29 (6): 1371-1379) teaches an anti-denatured collagen humanized antibody D93 that inhibits angiogenesis and tumor growth. Brooks et al. (*Int. J. Radiat. Oncol. Biol. Phys.* 2002 Nov 15; 54 (4): 1194-1201) teaches ionizing radiation modulates the exposure of the HUIV26 cryptic epitope within collagen type IV during angiogenesis. Jo et al. (*Mol. Vis.* 2006 Oct 26; 12: 1243-1249) teaches a humanized version of HUIV26 designated H8, which has an inhibitory effect on choroidal neovascularization.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
May 21, 2007

Communication Re: Appeal	Application No.	Applicant(s)	
	09/995,529	WATKINS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☐ The Notice of Appeal filed on _____ is not acceptable because:

   (a) ☐ it was not timely filed.

   (b) ☐ the statutory fee for filing the appeal was not submitted. See 37 CFR 41.20(b)(1).

   (c) ☐ the appeal fee received on _____ was not timely filed.

   (d) ☐ the submitted fee of $_____ is insufficient. The appeal fee required by 37 CFR 41.20(b)(1) is $_____.

   (e) ☐ the appeal is not in compliance with 37 CFR 41.31(a)(1) in that no claim has been twice rejected.

   (f) ☐ a Notice of Allowability, PTO-37, was mailed by the Office on _____.

2. ☐ The appeal brief filed on _____ is NOT acceptable for the reason(s) indicated below:

   (a) ☐ the brief and/or brief fee is untimely. See 37 CFR 41.37(a).

   (b) ☐ the statutory fee for filing the brief has not been submitted. See 37 CFR 41.20(b)(2).

   (c) ☐ the submitted brief fee of $_____ is insufficient. The brief fee required by 37 CFR 41.20(b)(2) is $_____.

The appeal in this application will be dismissed unless corrective action is taken to timely submit the brief and requisite fee. See 37 CFR 41.37(a)(1). Extensions of time may be obtained under 37 CFR 1.136(a). See 37 CFR 41.37(e).

3. ☒ The appeal in this application is DISMISSED because:

   (a) ☐ the statutory fee for filing the brief as required under 37 CFR 41.20(b)(2) was not timely submitted and the period for obtaining an extension of time to file the brief under 37 CFR 1.136(a) has expired.

   (b) ☐ the brief was not timely filed and the period for obtaining an extension of time to file the brief under 37 CFR 1.136(a) has expired.

   (c) ☒ a Request for Continued Examination (RCE) under 37 CFR 1.114 was filed on *20 March 2007*.

   (d) ☐ other: _____.

4. ☐ Because of the dismissal of the appeal, this application:

   (a) ☐ is abandoned because there are no allowed claims.

   (b) ☐ is before the examiner for final disposition because it contains allowed claims. Prosecution on the merits remains CLOSED.

   (c) ☐ is before the examiner for consideration.